REMARKS

The claims have been renumbered according to the direction of the Examiner. Claims 48-53, 62-78, 80-88, 91-93, 96-98 and 100-114 are pending in this application. Of the currently pending claims, the Examiner allowed claims 48, 49, 64, 75-78, 80-83, 86-88, 92-93, and 98 in the most recent action. Claims 68-74 and 85 were objected to. The rejections that remain pertain to claims 50-53, 63, 65-74, 84, 85, 91, and 96-97. Support for new claims 102, 105, 108, and 109 can be found, e.g., at page 11, line 32.

Telephonic Conference of May 25, 2005

The Applicants thank the Examiner for the courtesy of the Telephonic Conference held on May 25, 2005. The Applicants' representatives discussed issues of the rejections in the office action, particularly issues of written description and enablement. The Applicants' position is further elaborated below.

As reflected in the Examiner's Interview Summary dated May 27, 2005, the Examiner requested that the Applicants clarify "what fragment of the human protein had actually been expressed, (i.e., what fragment is encoded by the PpuMI-NotI construct discussed at page 34 of the specification)." A Second Declaration of Jeffrey Browning, Ph.D. is submitted herewith to provide the requested information. As stated in this declaration, the protein encoded by the construct described on page 34 of the specification includes a fragment of human TRELL that corresponds to amino acids 100 to 284 of SEQ ID NO:4.

Drawings

The Office Action Summary did not indicate whether the drawings filed on 2/5/99 are accepted or objected to. Absent further clarification, the Applicants presume that they have been accepted.

Claim Objections

The claims have been renumbered according to the direction of the Examiner.

Claims 68-74 were objected to because a multiple dependent claim, claim 68, depended from another multiple dependent claim, claim 62. The Applicants have amended claim 68 to cure this objection.

Claim 85 was objected to as being ungrammatical. The Applicants have amended claim 85 to include the term "said," as suggested in the Office Action.

Rejections for 35 U.S.C. § 112; Second Paragraph - Indefiniteness

Claims 50, 53, 60, 62, 63, 65-67, 91, and 92 were rejected as indefinite. Claim 60 has been cancelled without prejudice.

Indefiniteness regarding "amino acid terminus"

The Office Action at page 4 states:

> **Claims 50, 91, and 92 are indefinite because it is unclear what is intended by "amino acid terminus beginning at any one of amino acids 81-139 of SEQ ID NO:4." The term "amino acid terminus" is not a term of art. The Examiner believes Applicant intended "amino terminus".**

The Applicants have amended the claims to refer to the "amino terminus" rather than the "amino acid terminus."

> **It is also unclear what is intended by a "terminus beginning at" because use of the word "beginning makes it unclear what is and is not intended to be embraced by the term "terminus."**

Claims 50, 51, 52, and 91 have been amended to clarify that the mentioned amino terminus refers to the first amino acid from SEQ ID NO:4 in an amino terminal truncation of SEQ ID NO:4. Claim 92 is cured by the amendment to claim 91.

Indefiniteness regarding "complement"

The Office Action alleges that:

> **Claims 53, 62, 63, and 65-67 dependents are indefinite in the recitation of "the complement of said coding sequence is selected from ... a) nucleotides 106-852 of SEQ ID NO:3 and b) nucleotides 241-852 of SEQ ID NO:3" because the SEQ ID NO:3 is not the complement of the coding sequence.**

The Applicants have amended claim 53 to correct the typographical error noted in the rejection. Because claims 62, 63, and 65-67 depend from claim 53, Applicants submit that the amendment to claim 53 overcomes the rejection with respect to these claims as well and that the rejection can be withdrawn.

Rejections for Alleged Lack of Written Description

The Office Action alleges that 51-53, 55, 58-63, and 65-67 are not supported by an adequate written description. Claims 55 and 58-61 are cancelled without prejudice. The Applicants reserve to traverse the rejection with respect to these claims in other applications or in subsequent prosecution of this application.

The Applicants respectfully traverse with respect to claims 51-53, 62-63, and 65-67.

Written Description Rejection of Claims 51-52

The Office Action first discusses the written description of claims 51-53. The rejection of claims 62, 63, 65, and 66 results from their dependency on these claims.

The Office Action alleges, on pages 6-7, that:

> **The specification discloses a single species of these claimed genuses, i.e., SEQ ID NO:3. Note that SEQ ID NO:2, which is a fragment of mouse TRELL, is less than 90% identical to SEQ ID NO:4, and so SEQ ID NO:1 is not a member of the genuses claimed in claims 51-53 because it does not encode a polypeptide that is at least 90% identical to SEQ ID NO:4.**
>
> **The specification discloses at page 36 that human TRELL has the property of inducing apoptosis in HT-29 cells. The specification fails to provide any guidance as to the relationship between the structure of TRELL and this function or any other disclosed function. In particular, there is no guidance as to how the sequence of the single disclosed species of the claimed genus can be varied while still retaining its function, and no specific variants are given of any such variant. In view of the large number of conceivable variants in the claimed genus, and the failure to provide any correlation between the structure of TRELL and any function, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.**

The premise of the written description rejection appears to be that the specification fails to "reasonably convey to one skilled in the art , . . . that the inventors had possession of the

claimed invention." MPEP § 2163.04 states with respect to the written description requirement that:

> The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

The rejection for lack of written description made against claims 51 and 52, however, fails to meet this burden. The evidence proffered is that the mouse TRELL protein is less than 90% identical to human TRELL. However, this relationship makes clear that **the inventors were in possession of a genus much broader than one that only includes sequences 90% identical to human TRELL**. In fact, claims 51 and 52 are narrower in scope than the genus that the Applicants possessed.

The Applicants disclosed the relationship between human and mouse TRELL and thus revealed numerous other species that are within the scope of claims 51 and 52. In Figure 1, the specification provides the sequence listings and an alignment for the two TRELL proteins: SEQ ID NO:4 (which is 284 amino acids long) and SEQ ID NO:2 (which is 225 amino acids long). Over the 225 amino acids of SEQ ID NO:2, the two sequences have identical residues at 198 positions (88% identity). Of the 27 residues that differ between the sequences, seven of these positions have conserved substitutions, while twenty have non-conservative substitutions, according to the specification's terms (see, e.g., pages 18-20). Thus, the specification teaches, at a minimum, 27 examples of residues in SEQ ID NO:4 that are likely to tolerate either non-conservative substitutions or conservative substitutions, as the case may be. One skilled in the art would readily recognize TRELL proteins that include, for example, one, two, or more substitutions of human TRELL residues with the corresponding residues from the mouse TRELL protein. Such proteins would be at least 90% identical to SEQ ID NO:4.

The Applicants respectfully submit that the Examiner has not shown by the preponderance of the evidence that "a person skilled in the art would not recognize . . .a description of the invention defined by" claims 51 and 52. To the contrary, as explained above, the specification does provide guidance on allowable variations and shows that the Applicants

were in possession of the genera of nucleic acids claimed in claims 51 and 52. Accordingly, there is an adequate written description to support claims 51 and 52 and claims that depend therefrom (in particular claims 62-63 and 65-67).

Written Description Rejection of Claim 53

The Examiner rejected claim 53 for lack of written description. According to the Examiner:

> **Claim 53 and dependents are drawn to a nucleic acid that hybridizes under high stringency conditions to bases 106-852 or 241-852 of SEQ ID NO:3. . . .**
>
> **The specification discloses a single species of these claimed genuses, i.e., SEQ ID NO:3.**

The above reasons in support of the written description of claims 51 and 52 also pertain here. Nucleic acids encoding variants of SEQ ID NO:3 that have conservative and non-conservative mutations can easily be made by changing a handful or fewer nucleotides. Such nucleic acids would hybridize under the specified conditions to referenced fragments of SEQ ID NO:3 and illustrate possession of a genus of nucleic acid species within the scope of claim 53.

Even were it not the case, a single species supports a claim to a genus of nucleic acids that hybridize under high stringency conditions. Example 9 of the Synopsis of Application of Written Description Guidelines (1999)[1] endorses the use of hybridization claims in an example with even a single species (page 35 et seq.). In Enzo Biochem, Inc. v. Gen-Probe Inc., the Federal Circuit took judicial notice of the Guidelines and the "Synopsis of Application of Written Description Guidelines." 323 F.3d 956, 967 (Fed. Cir. 2002). Referring to Example 9 of the Synopsis, the court stated, "[the PTO] determined that such claims may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Id.

Accordingly, there is an adequate written description for claim 53, and for claims dependent therefrom. New claim 111 depends from claim 53 and refers to nucleic acids in

[1] available at http://www.uspto.gov/web/offices/pac/writtendesc.pdf .

which the polypeptide is capable of binding to an HT-29 colon carcinoma cell and inducing apoptosis in said carcinoma cell.

Rejections for Alleged Lack of Enablement

The Office Action alleges that claims 51-53, 55, 58-63, 65-67, 84, 96, and 97 are not enabled. Claims 55 and 58-61 are cancelled without prejudice. The Applicants reserve the right to traverse the rejection with respect to these claims in other applications or in subsequent prosecution of this application.

The Applicants respectfully traverse with respect to claims 51-53, 62-63, 65-67, 84, 96, and 97.

Rejection of claims 51-53, 62-63, and 65-67 for lack of enablement

The Examiner maintains that the specification "does not reasonably provide enablement for nucleic acid molecules encoding variants of SEQ ID NOS:2 and 4." The Applicants respectfully traverse. The Examiner begins by characterizing claims 51, 52, 58, 59, 53, 60, and 61 and notes, on page 10:

> **Thus, the claims embrace nucleic acids encoding polypeptide that may vary substantially from the disclosed amino acid sequences of SEQ ID NOS:2 and 4.**

To the contrary, the claims do not require substantial variation, but instead require very substantial *identity*. With respect to claims 51 and 52, the claims require at least 90% identity, a degree of identity greater than the genus possessed by the Applicants at the time of filing. As discussed above, the Applicants possessed sequences (e.g., SEQ ID NO:2 and 4) that differed by greater than 90%, but have defined the scope of claims in narrower terms.

With respect to claim 53, the Federal Circuit, in Enzo, has characterized hybridization under high stringency as "[a condition that] dictate[s] that all species within the genus will be structurally similar." 323 F.3d 956, 967 (Fed. Cir. 2002). Thus, high stringency hybridization is not unbounded language that captures substantial variations, as suggested by the Office Action

(as quoted above), but rather language that defines a very limited and permissible level of variation.

On page 11, the Examiner contends further that:

> **In view of the variety of structures and functions within the TNF-related cytokine family, and the lack of guidance regarding the structure and function of SEQ ID NOS:2 and 4, it is highly unpredictable as to how amino acid substitution will affect the functions of SEQ ID NOS:2 and 4.**

As discussed above, the Applicants have disclosed the relationship between human and mouse TRELL that provides guidance as to which amino acid substitutions may be tolerated. In Figure 1, the specification provides the sequence listings and an alignment for the two TRELL proteins: SEQ ID NO:4 and SEQ ID NO:2. Over the 225 amino acids of SEQ ID NO:2, the two sequences have identical residues at 198 positions (88% identity). The alignment in Figure 1 teaches examples of amino acids substitutions that produced by natural evolution. Of the 27 residues that differ between the sequences, seven of these positions have conserved substitutions, while twenty have non-conservative substitutions. Thus, the specification teaches multiple examples of residues in a protein that are likely to tolerate non-conservative substitutions and examples of residues that are likely to tolerate conservative substitutions. These examples provide more than adequate guidance for the genera defined by claims 51 and 52.

In framing the rejection, the Examiner relies in part on Ngo et al., at page 12:

> **Ngo et al. taught that, "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm." [emphasis added]**

However, Ngo is referring to deducing the tertiary structure of a protein from its amino acid sequence "alone." Tertiary structure is the three dimensional structure, for example, as determined by modelling, X-ray crystallography, or NMR. Enablement under § 112 does not require the disclosure of the tertiary structure of a protein. Even so, skilled readers of this application do not need to predict the structure of TRELL proteins because the application teaches, e.g., at page 14 and 3, that these proteins are TNF family members that are structured as "a sandwich of two anti-parallel β-pleated sheets with the 'jelly roll' or Greek key topology."

The Examiner further relies on Rudinger, at page 12:

Rudinger taught that, "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." [emphasis added]

Rudinger is clearly not applicable here since there is no requirement for one skilled in the art to predict *a priori* the significance of particular amino acids. Instead, the disclosure (e.g., at Figure 1) teaches the significance of many amino acids, particular those which are conserved between human and mouse at the level of identity, those which are related by conservative substitutions, and those which are related by non-conservative substitutions.

While it may be true that in some instances a single amino acid substitution can affect the function of a polypeptide, it also recognized in the art that, for any given protein, many residues can be substituted without affecting a specified function. This much is exemplified by Applicants' own disclosure of SEQ ID NO:2 and 4, and by the prior art. See, e.g., Bowie et al. (1990) *Science* 247:1306-1310 (copy enclosed), an article published some 14 years after Rudinger. At page 1306, lines 12-13, Bowie teaches that "proteins are surprisingly tolerant of amino acid substitutions". Bowie et al. cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (Bowie at page 1306, col. 2, lines 14-17). Presumably the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on Bowie et al.'s teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity.

These odds are far better than those at issue in In re Wands, 858 F.2d 731 (Fed. Cir. 1988), in which the court said that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question then is not whether it is possible to predict for each possible mutation whether it can be tolerated, but rather whether one of ordinary skill can produce, without undue experimentation, species in which the activity is not abolished. Based on Bowie et al.'s teachings, one would predict that even random substitution of residues in SEQ ID NO:4 will predictably result in a majority of the species having full or partial activity,

for example, either as a polypeptide capable of binding to a HT-29 colon carcinoma cell and inducing apoptosis in said HT-29 colon carcinoma cell or as an antigen.

In sum, at a time when that art of protein mutagenesis had attained a high degree of sophistication, the application provides at least two exemplary polypeptides, exemplary instructions on how mutate, evaluate, and use polypeptides as well as an alignment which conveys to readers skilled in the art the range of naturally tolerated variation. From this disclosure, one skilled in the art, using routine methods without undue experimentation, would be able to make and use nucleic acids within the scope of claims 51 and 52. These claims are clearly enabled, as are claims 62-63, and 65-67, which depend from claims 51 and 52.

Rejection of claims 84, 96, and 97 for lack of enablement

The Applicants do not accede to the basis of the Examiner's rejection, but have amended claim 84 to recite the term "isolated" merely to expedite prosecution. The amendment is made without prejudice to the subsequent prosecution of claims to host cells not limited by the term.

Conclusion

The Applicants respectfully submit that all claims are in condition for allowance. The Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do the Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

The Applicants also thank the Examiner for noting the allowability of claims in this application and previously pending claims as stated in the Notice of Allowance mailed April 26, 2004. With respect to the stated "Reasons for Allowance," the Applicants note that the claims are enabled for uses in addition to those identified by the Examiner and read the Examiner's remarks as consistent with this view.

All amendments and cancellations are made without prejudice and disclaimer and may be made for reasons not explicitly stated or for reasons in addition to ones stated.

Enclosed is Petition for Extension of Time and a $450 check for the fee. Please apply any charges, including any fee required to maintain the pendency of this application, to deposit account 06-1050, referencing Attorney Docket No. 10274-107001.

Respectfully submitted,

Date: 27 June 2005

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